JOC The Journal of Organic Chemistry

Article

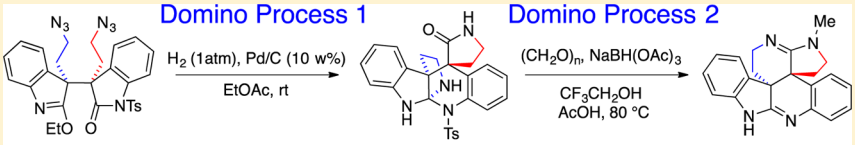
pubs.acs.org/joc

An Efficient Synthesis of (±)-Dehaloperophoramidine

Anita Hoang, Kirill Popov, and Peter Somfai*

Centre for Analysis and Synthesis, Department of Chemistry, Lund University, 22100 Lund, Sweden

Supporting Information



ABSTRACT: Perophoramidine and communesin F are structurally related indole alkaloids with an intriguing polycyclic core containing vicinal all-carbon quaternary stereocenters. Dehaloperophoramidine is a dehalogenated synthetic analogue of perophoramidine. Synthetic studies toward the total synthesis of dehaloperophoramidine have led to the discovery of two novel domino processes, the first encompassing four steps and resulting in the formation of an *ortho*-amide. A thorough study of the reactivity of the *ortho*-amide functionality revealed the second domino reaction and ultimately yielded the target molecule. The vicinal all-carbon quaternary stereocenters having *trans* relative stereochemistry are constructed early in the reaction sequence by employing Overman's samarium mediated reductive dialkylation procedure. Described are the synthetic studies that led to the final eight-step synthesis of dehaloperophoramidine.

INTRODUCTION

Perophoramidine (**2**) exists naturally in marine ascidian *Perophora namei* and was demonstrated to be active against the HCT116 colon carcinoma cell line with an IC_{50} of 60 μm (Figure 1).[1] The unique polycyclic core of this alkaloid is

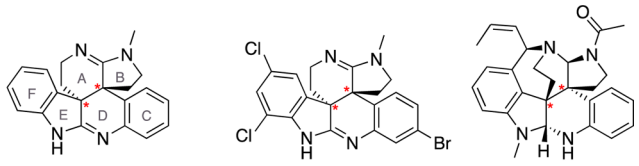


Figure 1. Structurally related indole alkaloids dehaloperophoramidine (**1**), perophoramidine (**2**), and communesin F (**3**).

structurally related to the communesin series, e.g. communesin F (**3**) found in *Entermorpha intestinalis*, which have been shown to display moderate insecticidal activity against instar silkworms larvae.[2] Although perophoramidine (**2**) and the communesin alkaloids share similar carbon skeletal connectivity, the hexacyclic core of compound **2** contains halogenated aromatic rings, bis-amidine functionalities, and vicinal quaternary stereocenters having *trans* relative stereochemistry (indicated with stars). The communesin alkaloids, in turn, feature a bis-aminal motif and *cis* relative stereochemistry of the quaternary stereocenters. These structural challenges need to be addressed when pursuing a total synthesis of these molecules.[3] Not surprisingly, the intriguing architecture of these indoline alkaloids have aroused much interest in the synthetic community, which have resulted in a number of elegant syntheses.[4]

It was originally suggested that perophoramidine (**2**) is biosynthetically derived from an oxidative dimerization of two tryptamine units while **3** is formed from tryptamine and aurantioclavine,[5] and this notion was later confirmed by the characterization of the responsible biosynthetic gene cluster.[6]

Dehaloperophoramidine (**1**) is the dehalogenated synthetic analogue of **2** and was first reported in the original isolation paper.[1] In 2006, Rainier and co-workers utilized a thioindole spirocyclization methodology to efficiently form the A/C/D/E/F ring system of **1** together with one of the quaternary stereocenters, ultimately resulting in the total synthesis of the target compound in 18 steps.[7] Subsequently, Takemoto and co-workers reported an efficient dearomatizing conjugate addition−allylation strategy that installed the vic-quaternary stereocenters in a single operation and furnished **1** in 17 steps.[8] Most recently, Westwood and co-workers employed [3,3]-Claisen rearrangement and a subsequent epoxide opening/Sakurai allylation to install the vic-quaternary stereocenters and completed the total synthesis of **1** in 23 steps.[9] Herein, we report the evolution of our eight-step synthesis of dehaloperophoramidine (**1**).[10]

RESULTS AND DISCUSSION

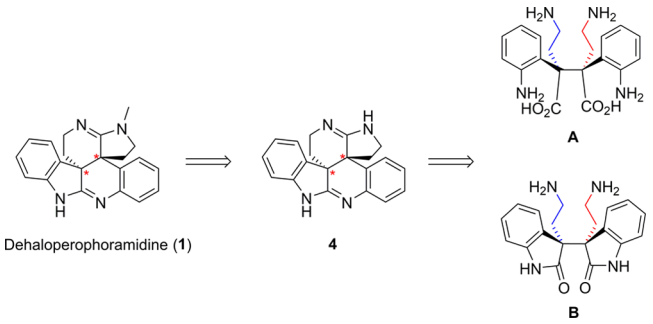
Since it has been suggested that perophoramidine (**2**) is biosynthetically derived by merging two identical precursors, this implies that some latent symmetry should be embedded in this structure as well as in dehaloperophoramidine (**1**).[11] Indeed, disconnecting four C−N bonds in **1** reveals the σ-symmetric structure **A**, or its obvious equivalent bis(oxindole)

Received: December 12, 2016
Published: February 1, 2017

DOI: 10.1021/acs.joc.6b02969
J. Org. Chem. 2017, 82, 2171−2176

B, which appeared to be an excellent foundation for our continued analysis (Scheme 1).

Scheme 1. Latent Symmetry of 1 Is Revealed When All Carbon−Nitrogen Bonds Are Disconnected[a]



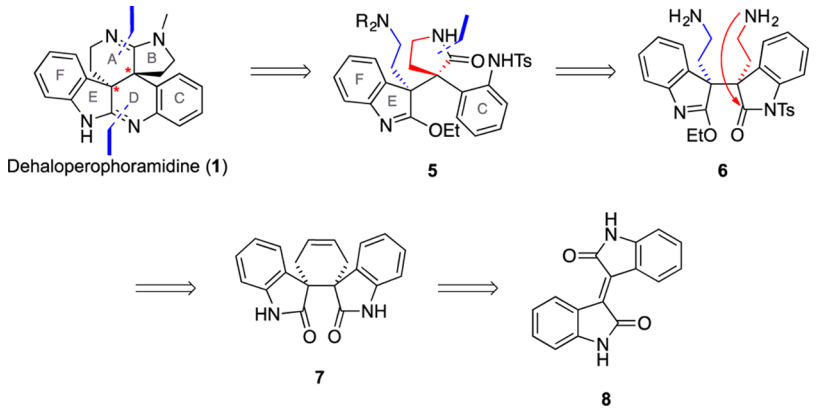
[a]Bisoxindole **B** is the synthetic equivalent to the σ-symmetric structure **A**.

Furthermore, our analysis was also dictated by the ambition to install all skeletal carbon atoms present in **1**, including the vicinal all-carbon stereocenters, and the required functional groups, in their correct oxidation state, early in the reaction sequence. Although perhaps counterintuitive, since such a strategy will result in a linear reaction sequence that sometimes is considered less efficient compared to convergent alternatives,[12] the intention was to allow for intramolecular proximity effects, which can facilitate novel domino reactions and increase the overall efficiency of the synthesis.[13] With this in mind, disconnection of the A and D ring amidines in **1** revealed compound **5**, which we envisioned to be derived from **6**, the synthetic equivalent of **B**, by a kinetically controlled differentiation of the aminoethyl moieties (Scheme 2). Compound **6** should be accessible from the commercially available isoindigo (**8**). The conversion of bis-amine **6** into lactam **5** might initiate a series of subsequent reactions, and at the beginning of this investigation it was not clear if this would provide an opportunity for uncovering a useful domino reaction or be problematic. In any case, we envisioned several possibilities for the conversion of **5** into the target molecule **1** and decided that the final decision would have to wait until **5** was secured.

Our synthesis commenced with the introduction of the vicinal quaternary stereocenters by subjecting **8** to Overman's SmI_2-mediated reductive dialkylation with *cis*-1,4-dichloro-2-butene to afford **7** as a single diastereomer and in high yield (Scheme 3).[14] It turned out, however, that this reaction was capricious with isolated yields of **7** varying from 10% to, at best, 68%, and this was eventually ascribed to the quality of the SmI_2 reagent. When using a freshly prepared and titrated reagent the dialkylation was reproducible and consistently gave a 68% yield of compound **7**.[15] When compound **8** is subjected to SmI_2 at rt, the corresponding dienolate is formed in less than 30 min, which is evident by isolation of dihydroisoindigo (98%) after hydrolytic workup. When instead *cis*-1,4-dichloro-2-butene was added after 30 min the formation of adduct **7** was observed together with isoindigo (**8**). It is believed that regeneration of **8** under the reaction conditions is a result of initial mono-alkylation of the dienolate followed by a competing E1cB reaction, instead of the desired alkylation to form **7**.[14] The reaction temperature affected the reaction outcome, and the optimal results were obtained at 0 °C; at higher reaction temperatures the **7**/**8** ratio decreased while performing the reaction below 0 °C did not improve the situation.

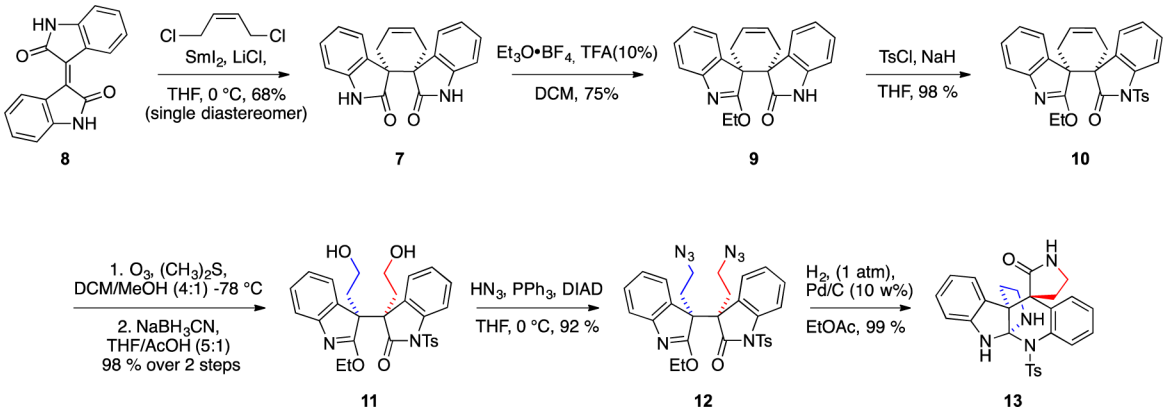
Initially, compound **7** was desymmetrized by formation of the corresponding *N*-Ts imide. The yield for this step was, however, far from optimal with only 42% (72% brsm) of the desired product being isolated, the low yield being a consequence of considerable amounts of the corresponding bis *N*-Ts product being formed. The efficiency of the desymmetrization could be improved to 75% by instead forming the monoimidate using Meerwein's reagent and a catalytic amount of TFA.[16] It is believed that the improved selectivity of the monoalkylation is ascribed to the slow conformational equilibria of the cyclohexene moiety in **7**, which is evident from the broad peaks in its ^{1}H NMR spectrum. Alkylation of the equatorial carboxamide moiety is believed to be more favored than alkylation of the axial one for steric reasons. Thus, once the first imidate is formed, the second alkylation must take place on an axial carboxamide group, which is less favorable, resulting in a selective monoalkylation. Since the *N*-substitiuents in **7** are projected away from the cyclohexene ring, the formation of the *N*-Ts imide or bis imide is not expected to experience much steric differentiation. With the monoimidate **9** in hand, subsequent tosylation provided compound **10**. A one-pot ozonolysis/reduction of this material was followed by a Mitsunobu reaction[17] with HN_3 to furnish bis(azide) **12**, which set the stage for the subsequent differentiation of the aminoethyl side-chains. In the event, hydrogenation of compound **12** initiated a domino process that resulted in the formation of the hexacyclic *ortho*-amide **13**, the

Scheme 2. Retrosynthetic Analysis of 1

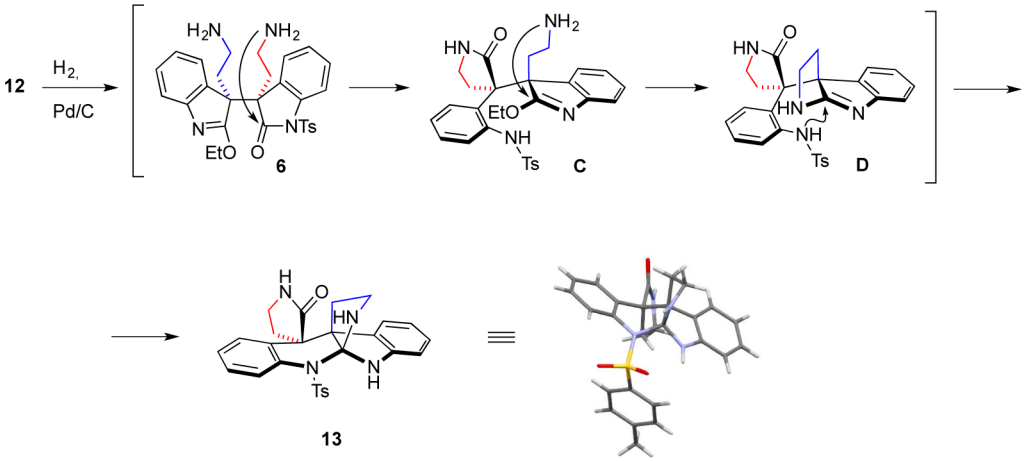


DOI: 10.1021/acs.joc.6b02969
J. Org. Chem. 2017, 82, 2171−2176

Scheme 3. Synthesis of *ortho*-Amide 13 from Commercially Available Isoindigo 8



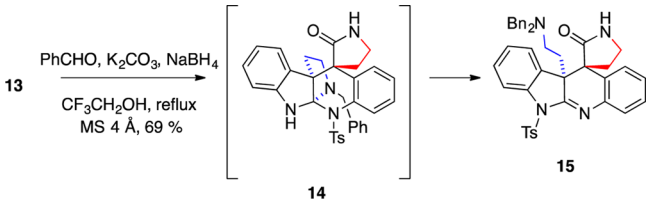
Scheme 4. Tentative Mechanism of the Domino Reaction Leading to *ortho*-Amide 13



structure of which was confirmed by X-ray crystallography. Although the formation of *ortho*-amide **13** was unexpected, it secured our original goal of differentiating the aminoethyl side-chains with concomitant formation of the B and D rings. This domino process is believed to involve initial reduction of diazide **12** to furnish diamine **6** followed by a kinetically controlled ring closure to furnish compound **C** in which the B ring lactam has been installed (Scheme 4).[18] Subsequent addition of the remaining aminoethyl side chain to the imidate moiety yields amidine **C**, which is then trapped by the proximate sulfonamide to form the D ring, resulting in *ortho*-amide **13**.

At this point, our plan was to selectively disconnect the aliphatic amine in *ortho*-amide **13** with concomitant formation of the D/E amidine functionality or, alternatively, the corresponding aminal. Initial attempts to reduce compound **13** to the corresponding aminal using a variety of reaction conditions ($NaBH_4$, $NaBH_3CN$, and DIBALH) only returned the starting material with the *ortho*-amide moiety unaffected. Eventually, it was found that subjecting compound **13** to benzaldehyde and sodium borohydride in trifluoroethanol furnished amidine **15** in good yield (Scheme 5).[19] It is believed that this transformation proceeds by initial reductive amination of the aliphatic amine moiety in **13** followed by an additional reductive alkylation of this position to give the corresponding amidine. Finally, the so formed *N*-Ts amidine participates in a 1,3-sulfur shift to furnish the D/E amidine system **15**.[20] This notion is supported by the isolation of the *N*-alkylated amidine

Scheme 5. Reductive Alkylation of *ortho*-Amide 13

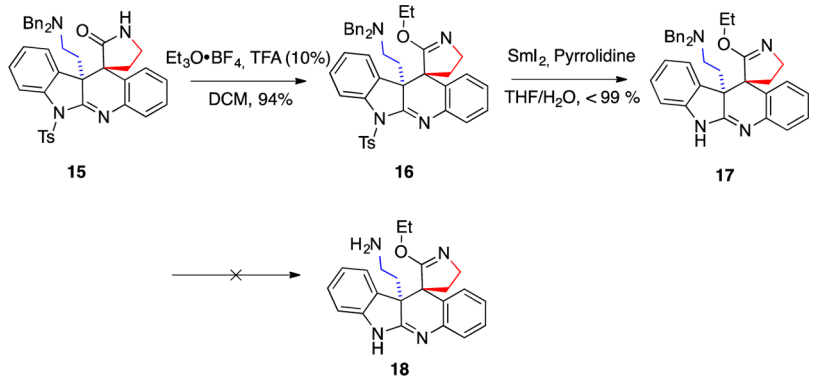


14 in the reaction of **13** with benzaldehyde and its subsequent conversion into amidine **15**.

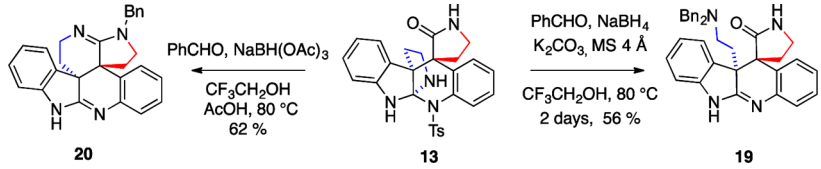
At this stage, a route from lactam **15** to dehaloperophoramidine (**1**) involving imidate formation of the B ring lactam, removal of the benzyl protecting groups followed by cyclization of the A ring, and detosylation to give *N*-demethyl dehaloperophoramdinine (**4**) appeared obvious. The regioselective *N*-methylation of **4**, or its protected precursor, to afford **1** was, however, of considerable concern since previous studies have indicated that the regioselectivity in such a transformation can be rather poor.[4a] In the event, compound **15** was treated with Meerwein's salt in the presence of catalytic amounts of TFA to furnish imidate **16** in good yield (Scheme 6).[16] Removal of the *N*-Ts group, using SmI_2 and pyrrolidine in THF/H_2O,[21] provided compound **17** in excellent yield. However, deprotection of the benzyl groups through hydrogenation proved to be problematic. Attempts using various catalysts (Pd/C, $Pd(OH)_2/C$) in different solvent mixtures as well as performing the reaction at different pressures gave none

DOI: 10.1021/acs.joc.6b02969
J. Org. Chem. 2017, 82, 2171−2176

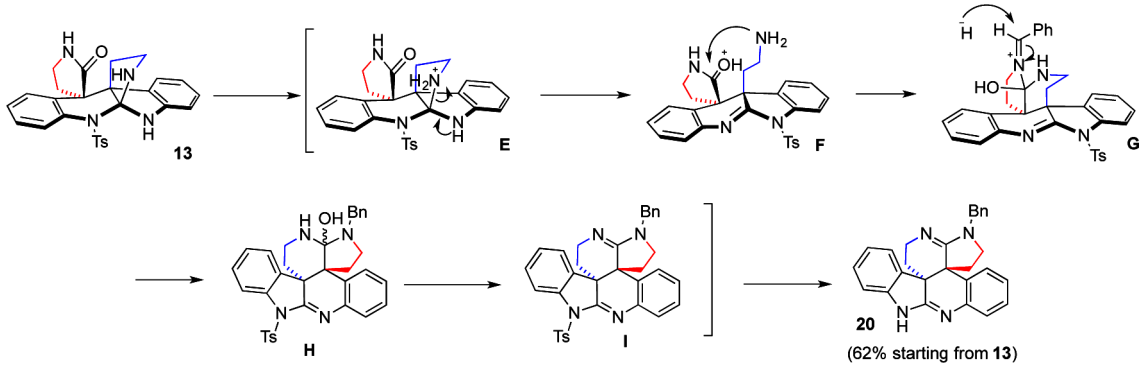
Scheme 6. Initial Attempts To Form the A/B Amidine



Scheme 7. Selective Conversion of *ortho*-Amide 13 into Amidine 19 or the Hexacyclic Structure 20



Scheme 8. Proposed Mechanism of the Domino Transformation of 13 into 20



of the expected **18** and only resulted in isolation of the starting material together with the monodebenzylated product.

In a parallel line of this investigation it was found that performing the reductive amination/ring opening on *ortho*-amide **13** under prolonged reaction times afforded the detosylated D/E amidine **19** (Scheme 7). After considerable experimentation it was also shown that subjecting *ortho*-amide **13** to reductive amination under acidic conditions (PhCHO, $NaBH(OAc)_3$, AcOH, CF_3CH_2OH) resulted in the formation of *N*-Bn-bis(amidine) **20** as a single regioisomer, the structure of which was confirmed by X-ray crystallographic analysis. Compound **20** contains the hexacyclic structure of dehaloperophoramidine (**1**), the difference being that the B ring is *N*-benzylated instead of *N*-methylated as in the target compound.

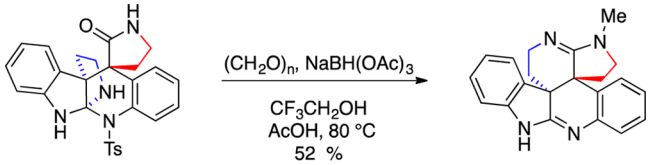
In this domino process the *ortho*-amide **13** is converted into the D/E amidine, the A ring is formed with subsequent formation of the A/B amidine, the A ring is *N*-benzylated, and the *N*-Ts group participates in a 1,3-sulfur shift which is then followed by hydrolysis of the sulfonamide.

The conversion of *ortho*-amide **13** into the *N*-benzylated derivative **20** increases the overall efficiency of the synthesis and obviates our initial concern about the late stage regiselective alkylation of the A/B amidine. It is believed that the domino process (Scheme 8) commences with the protonation of *ortho*-amide **13**, which enables elimination of the aliphatic amine moiety to afford protonated lactam **F**. The primary amino-ethyl side chain then participates in a cyclization, to install the A ring, followed by a reductive amination, affording intermediate **H**. The regioselectivity in the reductive amination, occurring preferentially on the B ring, is ascribed to the faster rate of formation of an iminium ion from pyrrolidine than from piperidine.[22] Subsequent dehydration of **H** under the acidic reaction conditions furnished intermediate **I**. Finally, hydrolysis of this species gave **20**. It was possible to isolate intermediate **H**, in which the 1,3-sulfur shift has already occurred, and subjecting it to acidic reaction conditions (AcOH, CF_3CH_2OH) resulted in clean conversion into **I**. Additional support for this mechanistic proposal was obtained by subjecting *ortho*-amide **13** to identical reaction conditions, resulting in complete recovery of the starting material and indicating that the reductive amination takes place before the formation of the *A*/*B* amidine moiety.

Next this domino transformation was applied for the synthesis of dehaloperophoramidine (**1**). Subjecting *ortho*-amide **13** (1.00 g scale) to paraformaldehyde under identical reaction conditions afforded **1** in 52% yield (0.350 g, Scheme 9) and completed our eight-step synthesis of the target molecule starting from isoindigo (**8**) in 23% overall yield.

DOI: 10.1021/acs.joc.6b02969
J. Org. Chem. 2017, 82, 2171−2176

Scheme 9. Completion of the Synthesis of Dehaloperophoramidine 1



13 1

CONCLUSIONS

We have developed a concise and efficient total synthesis of dehaloperophoramidine (**1**) in 23% overall yield over eight steps. In an effort to increase the synthesis efficiency, at the design stage it had already been decided that all skeletal carbon atoms should be introduced early in the synthesis, and the same argument was applied for having all functional groups in the correct oxidation state already from the start. In the course of the work, two new domino reactions were encountered that significantly improved the overall synthesis efficiency. The possibility of the first domino process, **12** → **13**, was realized already at the planning stage of the synthesis, while the discovery of the second, **13** → **1**, was unexpected and the result of a thorough examination of the reactivity embedded in *ortho*-amide **13**. It is believed that the thermodynamic preferences for the hexacyclic ring system present in **1** are the premise for the successful implementation of our synthesis.[5] Consistent with this reasoning, when similar chemistry was applied to the diastereomer of **7**, the diastereomer of **1** was not obtained but rather structures related to the chimonanthine ring system.[23]

EXPERIMENTAL SECTION

Experimental procedures and characterization data for the preparations of compounds **7**, **10**–**13**, **H**, **I**, **15**, **20**, and **1** have been reported previously.[9]

General. Unless otherwise stated, all reactions were performed under an inert atmosphere. Analytical thin-layer chromatography was performed with Merc Silica gel 60. Flash silica gel column chromatography was performed with Acros silica gel 40–60. High resolution mass spectra (HRMS) were recorded on Waters XEVO-G2 QTOF with electrospray ionization (ESI).

General Procedure for the TFA-Mediated Amide Alkylation. To a solution of amide (1 equiv) and TFA (10 mol %) in DCM (0.04 M) was slowly added $Et_3O{\cdot}BF_4$ (1.2 equiv) at 0 °C. The reaction was allowed to slowly warm to rt and stirred at that temperature, and the reaction was monitored by TLC analysis. The reaction was quenched with H_2O and extracted with DCM (3×). The combined organic phases were washed with brine and dried ($MgSO_4$). Concentration under reduced pressure afforded the crude alkyl imidate, which was purified by column chromatography on silica.

(2′R,3S*)-2-Ethoxydispiro[indole-3,1′-cyclohexane-2′,3″-indolin]-4′-en-2″-one (**9**).* The imidate formation was carried out according to the general procedure with **7** (980 mg, 3.1 mmol) and TFA (24 μL, 0.31 mmol), $Et_3O{\cdot}BF_4$ (730 mg, 3.72 mmol) in DCM (30 mL). The crude material was purified (*n*-heptane/EtOAc (1:2)) and gave **9** (805 mg, 2.34 mmol, 75%) as a white amorphous solid. Compound **9** exists as rotamers in $CDCl_3$ as seen by ^1H and ^{13}C NMR. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.57 (s, 2H), 7.45–7.31 (m, 1H), 7.30–7.00 (m, 6H), 6.77 (s, 2H), 6.72–6.47 (m, 1H), 6.32–5.83 (m, 2H), 5.65 (s, 2H), 4.87–4.39 (m, 2H), 4.38–4.12 (m, 2H), 3.64–3.15 (m, 1H), 2.99–2.78 (m, 1H), 2.19–1.89 (m, 1H), 1.69 (s, 3H), 1.50 (s, 2H), 1.19 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 182.0, 181.3, 178.6, 170.0, 153.8, 153.5, 142.1, 141.4, 139.4, 137.1, 133.0, 130.2, 126.0, 125.6, 124.7, 123.7, 123.6, 123.3, 122.4, 121.8, 121.5, 118.7, 118.4, 110.0, 109.3, 98.2, 67.2, 66.9, 66.6, 65.5, 65.3, 60.7, 59.8, 58.2, 53.9, 52.8, 50.8, 48.4, 33.3, 32.7, 31.5, 31.4, 30.8, 29.1, 27.0, 23.8, 23.5, 21.5, 20.2, 14.1, 13.9, 13.7. HRMS (ESI/TOF-Q) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{20}N_2O_2$ 345.1603; found 345.1605.

(3R,5a′R*,10b′S*)-14′-Benzyl-5′-tosyl-5′H,6′H-spiro[pyrrolidine-3,11′-[5a,10b](epiminoethano)indolo[2,3-b]quinolin]-2-one (**14**).* To a mixture of **13** (100 mg, 0.20 mmol) and K_2CO_3 (21 mg, 0.15 mmol) in CF_3CH_2OH (4 mL) was added benzaldehyde (21 μL ml, 0.20 mmol) in five portions, with each portion followed by a corresponding $NaBH_4$ (8 mg, 0.20 mmol). The mixture was heated to reflux for 8 h and then concentrated in vacuo. The resulting solid was dissolved in DCM (5 mL), washed with H_2O (3 mL) and brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by coloumn chromatography Et_2O/Heptane/$iPrNH_2$ (75:20:5), to give **14** as a white amorphous solid (12 mg, 10%): R_f = 0.30 (EtOAc/*n*-Heptane 1:2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.46–7.40 (m, 1H), 7.33–7.29 (m, 1H), 7.28–7.19 (m, 5H), 7.19–7.09 (m, 3H), 7.07 (d, *J* = 7.1, 1.0 Hz, 1H), 6.79–6.66 (m, 2H), 6.20 (s, 1H), 5.90 (s, 1H), 4.82 (d, *J* = 13.6 Hz, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 2.64–2.53 (m, 1H), 2.52–2.43 (m, 1H), 2.30 (s, 3H), 2.28–2.16 (m, 2H), 2.10–2.03 (m, 1H), 1.99–1.90 (m, 1H), 1.57–1.48 (m, 1H), 0.89–0.78 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 143.1, 139.2, 137.9, 136.4, 135.5, 129.5, 129.0, 128.9, 128.8, 128.1, 128.1, 127.8, 127.6, 126.6, 126.3, 126.2, 123.6, 119.0, 107.5, 104.6, 69.4, 52.1, 49.5, 48.4, 38.2, 33.3, 30.2, 29.62, 21.3. HRMS (ESI/TOF-Q) *m*/*z*: $[M + H]^+$ calcd for $C_{34}H_{32}N_4O_3S$ 577.2273; found 577.2273.

N,N-Dibenzyl-2-((10bS,11R*)-2′-ethoxy-6-tosyl-4′,5′-dihydrospiro[indolo[2,3-b]quinoline-11,3′-pyrrole]-10b(6H)-yl)ethan-1-amine (**16**).* The imidate formation was carried out according to the general procedure with **15** (50 mg, 0.08 mmol) and TFA (0.6 μL, 0.008 mmol), $Et_3O{\cdot}BF_4$ (17 mg, 0.09 mmol) in DCM (3 mL). The crude material was purified (isopropylamine/*n*-heptane/EtOAc (5:20:75)) and gave **16** (49 mg, 0.07 mmol, 94%) as a white amorphous solid: R_f = 0.52 (Et_2O/*n*-Heptane/*i*PrNH$_2$ 75:20:5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.43–7.34 (m, 2H), 7.32–7.26 (m, 1H), 7.25–7.11 (m, 10H), 7.08–7.00 (m, 4H), 7.01–6.92 (m, 2H), 6.86 (d, *J* = 7.4 Hz, 1H), 4.49–4.33 (m, 2H), 3.29 (d, *J* = 13.6 Hz, 2H), 3.21 (d, *J* = 13.6 Hz, 2H), 3.11 (ddd, *J* = 13.9, 8.4, 5.3 Hz, 1H), 2.66 (ddd, *J* = 13.8, 8.4, 5.1 Hz, 1H), 2.32 (s, 3H), 2.20–2.05 (m, 2H), 1.70–1.61 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H), 1.04 (ddd, *J* = 13.3, 8.4, 5.1 Hz, 2H), 0.52 (ddd, *J* = 13.4, 8.4, 5.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 168.7, 155.0, 145.1, 139.2, 135.2, 135.0, 135.0, 131.8, 129.8, 128.9, 128.7, 128.2, 127.8, 127.1, 126.8, 126.3, 125.9, 124.7, 121.5, 119.4, 64.8, 60.9, 58.2, 56.4, 51.3, 48.2, 35.1, 29.0, 21.8, 14.8. HRMS (ESI/TOF-Q) *m*/*z*: $[M + H]^+$ calcd for $C_{43}H_{42}N_4O_3S$ 695.3056; found 695.3060.

N,N-Dibenzyl-2-((10bS,11R*)-2′-ethoxy-4′,5′-dihydrospiro-[indolo[2,3-b]quinoline-11,3′-pyrrole]-10b(6H)-yl)ethan-1-amine (**17**).* To a solution of **16** (20 mg, 0.029 mmol) in THF were added H_2O (15 μL, 0.86 mmol) and pyrrolidine (48 μL, 0.058 mmol). A solution of SmI_2 in THF (3.6 mL, 0.08 M, 0.29 mmol) was added with a syringe pump (2 mL/min). The blue color of SmI_2 disappeared upon addition to the reaction mixture. The reaction was stirred for 3 h at rt and quenched by being poured into $Na_2S_2O_4$ (sat. aq.) and extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with H_2O (2 × 5 mL) and brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure afforded pure **17** (15 mg, 0.028 mmol <99%): R_f = 0.4 (Et_2O/Heptane/iPrNH$_2$ 75:20:5); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.18 (m, 3H), 7.18–7.11 (m, 6H), 7.11–7.05 (m, 4H), 7.04–6.98 (m, 2H), 6.97–6.89 (m, 3H), 4.62–4.29 (m, 2H), 3.46–3.23 (m, 5H), 3.16–2.99 (m, 1H), 2.42–2.08 (m, 3H), 1.90–1.65 (m, 3H), 1.51 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 170.6, 153.5, 138.9, 138.5, 133.3, 128.7, 128.7, 128.2, 128.0, 128.0, 127.0, 126.6, 126.4, 123.4, 122.7, 122.2, 118.1, 114.9, 64.6, 57.8, 57.4, 54.6, 51.5, 48.2, 36.5, 28.7, 14.8. HRMS (ESI/TOF-Q) *m*/*z*: $[M + H]^+$ calcd for $C_{36}H_{36}N_4O$ 541.2967; found 541.2969.

(10bS,11R*)-10b-(2-(Dibenzylamino)ethyl)-6,10b-dihydrospiro-[indolo[2,3-b]quinoline-11,3′-pyrrolidin]-2′-one (**19**).* To a mixture of **13** (390 mg, 0.81 mmol) and K_2CO_3 (111 mg, 0.57 mmol) in CF_3CH_2OH (16 mL) was added benzaldehyde (82 μL, 0.81 mmol) in

DOI: 10.1021/acs.joc.6b02969
J. Org. Chem. 2017, 82, 2171–2176

five portions, each portion followed by a corresponding $NaBH_4$ (30 mg, 0.81 mmol). The mixture was heated to reflux for 2 days and then concentrated in vacuo. The resulting solid was dissolved in DCM (20 mL), washed with H_2O (2*5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by coloumn chromatography (Et_2O/Heptane/$iPrNH_2$ (75:20:5)), to give **19** as a white amorphous solid (234 mg, 56%): R_f = 0.35 (Et_2O/Heptane/$iPrNH_2$ 75:20:5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.34 (m, 1H), 7.26−7.17 (m, 4H), 7.16−7.05 (m, 11H), 7.00−6.87 (m, 3H), 3.35 (d, J = 13.6 Hz, 2H), 3.28 (d, J = 13.6 Hz, 2H), 3.11 (td, J = 8.7, 5.5 Hz, 1H), 2.80 (td, J = 8.7, 5.8 Hz, 1H), 2.73−2.61 (m, 1H), 2.38−2.28 (m, 1H), 2.25−2.13 (m, 1H), 2.05−1.87 (m, 2H), 1.82−1.72 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 171.7, 139.3, 139.3, 133.2, 129.0, 128.9, 128.6, 128.1, 126.7, 126.6, 126.6, 123.9, 122.8, 122.7, 118.5, 115.2, 57.5, 54.7, 52.3, 47.9, 39.2, 33.1, 26.7. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ calcd for $C_{36}H_{38}N_4O$ 513.1654; found 513.2650.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02969.

Copies of ^1H and ^{13}C NMR spectra of new compounds, compound **I** and **1** (PDF)

Crystallographic data for **13**[24] (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: peter.somfai@chem.lu.se.

ORCID

Peter Somfai: 0000-0001-9416-1283

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Swedish Research Council, the Carl Tryggers Foundation, the Crafoord Foundation, the Swedish Institute, and Lund University.

■ REFERENCES

(1) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124−7126.

(2) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355−2358.

(3) (a) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 11943−11948. (b) Christoffers, J.; Baro, A. *Quaternary stereocenters: challenges and solutions for organic synthesis*; Wiley-VCH: Weinheim, 2005. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473−1482. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (e) Ling, T.; Rivas, F. *Tetrahedron* **2016**, *72*, 6729−6777. (f) Yu, X.; Hu, J.; Shen, Z.; Zhang, H.; Gao, J.-M.; Xie, W. *Angew. Chem., Int. Ed.* **2017**, *56*, 350−353.

(4) (a) Trost, B. M.; Osipov, M. *Chem. - Eur. J.* **2015**, *21*, 16318−16343 and references cited therein. (b) Zhang, D.; Song, H.; Qin, Y. In *Strategies and Tactics in Organic Synthesis*; Michael, H., Ed.; Academic Press: 2015; Vol. *11*, pp 377−408. (c) Lathrop, S. P.; Pompeo, M.; Chang, W. T. T.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 7763−7769.

(5) May, J. A.; Stoltz, B. *Tetrahedron* **2006**, *62*, 5262−5271.

(6) Lin, H. C.; Chiou, G.; Chooi, Y. H.; McMahon, T. C.; Xu, W.; Garg, N. K.; Tang, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 3004−3007.

(7) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317−4320.

(8) Ishida, T.; Ikota, H.; Kurahashi, K.; Tsukano, C.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 10204−10207.

(9) Wilkie, R. P.; Neal, A. R.; Johnston, C. A.; Voute, N.; Lancefield, C. S.; Stell, M. D.; Medda, F.; Makiyi, E. F.; Turner, E. M.; Stephen Ojo, O.; Slawin, A. M. Z.; Lebl, T.; Mullen, P.; Harrison, D. J.; Ireland, C. M.; Westwood, N. J. *Chem. Commun.* **2016**, *52*, 10747−10750.

(10) Popov, K.; Hoang, A.; Somfai, P. *Angew. Chem., Int. Ed.* **2016**, *55*, 1801−1804.

(11) Ho, T.-L. *Symmetry: a basis for synthesis design*; Wiley: New York, 1995.

(12) Hendrickson, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 5439−5450.

(13) (a) Martin, H. D.; Mayer, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 283−314. (b) Santra, S.; Andreana, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9418−9422.

(14) Link, J. T.; Overman, L. E. *J. Am. Chem. Soc.* **1996**, *118*, 8166−8167.

(15) Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem.* **2012**, *77*, 3049−3059.

(16) Popov, K.; Somfai, P. *J. Org. Chem.* **2016**, *81*, 3470−3472.

(17) But, T. Y. S.; Toy, P. H. *Chem. - Asian J.* **2007**, *2*, 1340−1355.

(18) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941.

(19) Tajbakhsh, M.; Hosseinzadeh, R.; Alinezhad, H.; Ghahari, S.; Heydari, A.; Khaksar, S. *Synthesis* **2011**, *2011*, 490−496.

(20) Bur, S. K. *Top. Curr. Chem.* **2007**, *274*, 125−171.

(21) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 503−506.

(22) (a) Brown, H. C. *J. Chem. Soc.* **1956**, 1248−1268. (b) Cook, A. G. *Enamines: synthesis, structure and reactions*, 2nd ed.; Marcel Dekker: New York, 1988.

(23) (a) Danielsson, J.; Somfai, P. *Org. Lett.* **2014**, *16*, 784−787. (b) Danielsson, J. Ph.D Thesis, Department of Chemistry, Lund University, February 2014. (c) Sanzone, A.; Somfai, P. *Eur. J. Org. Chem.* **2015**, *2015*, 3441−3449.

(24) CCDC 1432648 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

DOI: 10.1021/acs.joc.6b02969
J. Org. Chem. 2017, 82, 2171−2176